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Critical Reviews in Oncology/Hematology 87 (2013) 224–238

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

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The effect of estrogen on the sexual interest of castrated males: Implications to prostate cancer patients on androgen-deprivation therapy

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Accepted 16 January 2013

Contents

Abstract

Androgen deprivation therapy (ADT) for prostate cancer (PCa) treatment causes sexual dysfunction. We review here the effects of estrogen on the sexual performance of androgen-deprived males. The major findings are:

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1040-8428/$ – see front matter
http://dx.doi.org/10.1016/j.critrevonc.2013.01.006

1. Estrogen receptors are present in brain centers that are important for sexual behavior; as well as in male reproductive organs, in a pattern suggesting that estrogen may have some role in orgasmic function and genital skin sensitivity.
2. Estrogen restores sexual interest above castrate levels in many vertebrates including reptiles, birds and mammals; but multiple factors contribute to the magnitude of this effect.
3. Data from castrated men, aromatase-deficient men, male-to-female transsexuals, and men on antiandrogens all suggest that estrogen can maintain some libido in androgen-deprived men.

We discuss the general benefits of estrogen therapy to quality of life of men on ADT, the potential risks of this treatment, and possible treatment regimes for estrogen therapy in males. Unless contraindicated, we propose that PCa patients on ADT would benefit from supplemental parenteral estrogen.

Keywords: Androgen deprivation therapy; Prostate cancer; Libido; Estrogen; Male sexual function; Castrated animals; Orgasm; Skin sensitivity

1. Introduction

There are various situations where genetic males are therapeutically androgen-deprived. The most common reason for androgen deprivation therapy (ADT) is to slow down prostate cancer (PCa)'s growth. In addition, as part of sex reassignment surgery, male-to-female transsexuals (MtFs) are also androgen-deprived. ADT can be achieved by either surgical or chemical castration. Currently, luteinizing hormone-releasing hormone (LHRH) agonists are the most frequently used agents for ADT in the PCa patient population. However, other agents including high-dose estrogen (E), high-dose ketoconazole, abiraterone, and LHRH antagonists can also be used to achieve a castrate level of testosterone. Single-agent antiandrogen therapy is also used as a form of ADT, but does not lower serum testosterone levels.

In most cases, ADT impedes sexual function; reducing libido and causing erectile dysfunction [1]. These effects distress patients and psychologically impact their intimate partners, reducing the quality of life for both [2]. While treatments for erectile dysfunction are available, currently there is no treatment for loss of libido subsequent to ADT. Yet, loss of erections due to ADT does not mean a cessation in sexual activity [3]. For example, men can still achieve orgasm without an erect penis.

ADT not only depletes androgens in men, but also estrogens. This is because estrogen in males is derived from testosterone. Some males on ADT receive E therapy. For MtFs, E therapy can aid in body feminization (breast development) and, for PCa patients, supplemental E can alleviate some of the more intense adverse events, such as hot flashes [4]. Additional benefits of E treatment for androgen-deprived men include improving bone mineral density [5] and lipid profiles [6]. In one study, treatment with E also improved some aspects of cognitive function [7].

Previously we reviewed papers suggesting that E can, to some extent, elevate sexual interest in castrated males [8]. We have since confirmed this with a study of castrated male rats with and without estradiol (E2) treatment [9]. Here, we provide a more extensive literature review on how E influences sexual interest in androgen-deprived males for a wealth of species, ranging from amphibians to mammals including humans. In addition, we discuss the potential effect of E on peripheral tissues that are related to sexual function, such as genital skin and pelvic floor muscles that are important in achieving an orgasm. We then discuss the pros and cons of E therapy as well as various dosing regimes—factors that need to be considered in clinical settings.

2. Estrogen receptors

E induces its effects by acting on estrogen receptors (ERs) that are widely distributed throughout the body. In the tetrapod brain, ERs are present in areas that control male sexual behavior, most notably the medial preoptic area, medial amygdala and the bed nucleus of stria terminalis [10,11]. Intracranial E implants in those specific areas of the brain have been shown implicitly to increase sexual behavior in castrated males of many vertebrate species (see Suppl. Tables 1 and 2). The equivalent brain areas in humans also express ERs. Replicating the results observed in animals by implanting E into human brains would be excessively invasive; however, there is evidence that castrated men on E therapy maintain better libido than those not receiving supplemental E [8].

The mechanism for how E elevates sexual interest in castrated men has not been extensively investigated. In imaging studies, the preoptic area and medial amygdala are activated during sexual arousal by both visual [12] and olfactory stimulation [13,14] although not necessarily by tactile stimulation [15]. However, no study has explored if these activation patterns in response to sexual stimuli change after E treatment in androgen-deprived men.

E may also influence sexual behavior by acting on peripheral tissues. Indeed, ERs are present in male reproductive organs although their function remains enigmatic [16]. They may not be related to erectile function per se because in both castrated men and other male mammals, E treatment does not restore erectile function. We discuss in later sections how E may potentially modulate pelvic floor muscle function and genital skin physiology.

3. Estrogen and male sexual behavior

3.1. Animal studies

Dating back to the early 1900s, there were studies showing that ovarian grafts in capons [17] or injecting placental extract into castrated male rats [18] increased sexual activity. These were the first observations to suggest that female reproductive organs contained some substances that could positively influence sexual behavior in castrated males. The first natural estrogen, estrone, was identified in 1929–1930 and within a decade, Ball [19] provided the first direct evidence that E elevates male sexual interest by injecting estradiol benzoate (EB) into castrated male rats. Since then, studies on other species ranging from amphibians to mammals, have explored the effect of E on sexual behavior in castrated males (see Suppl. Tables 1 and 2), but rats remain by far the most studied species.

Administering E to castrated male rats increases mounting behavior, however, the extent to which E changes libido varied among studies (Suppl. Table 1). One factor likely to contribute to the varying results is the age at which castration is performed. Rats castrated at birth [20] or prepubertally [21] have less restoration in their sexual behavior than those castrated in adulthood [20,22]. This is likely because sexual differentiation of the brain, which first occurs during the perinatal period [23] then again during puberty [24], requires aromatizable androgen. Males castrated at birth or before puberty are not fully masculinized, resulting in less developed sexual behavior.

Other factors which may influence the effects of E on sexual behavior include the dose (e.g., [25]; [26] vs. [27]) and type of estrogen [28,29]. A dose too low (e.g., injection of $\leq$5 μg EB/day in rats) is not optimal in reinstating copulatory behavior. Interestingly, daily injection of high dose E restores all copulatory behaviors in castrated adult rats including ejaculation [30] even though the erectile reflex is not fully restored [31]. The mechanism to account for this is unclear since pelvic floor muscles, that are important for ejaculation, atrophy following castration, and E cannot restore their gross morphology [32].

The method of E administration is similarly an important factor in determining how extensively E raises sexual interest because different methods are associated with different fluctuations in plasma E2 levels. For example, daily injections of E lead to a sharp increase in plasma E2 levels that rapidly decline within 12 h [33]. Thus, several weeks of daily injections are required for males to reach the equivalent plasma E2 levels found in proestrous females [34]. In contrast, the use of a Silastic tube (i.e., slow-release implant) to administer E results in supraphysiological plasma E2 levels which stabilize to proestrous levels within 24 h [33]. However, the E2 content in the implanted tubes declines over time resulting in a gradual reduction in the plasma E2 levels over several weeks [34]. Thus, if sustained dosing is the goal, Silastic tubes containing E need to be replaced every several weeks.

Different methods of E administration are reflected in difference in the male rats' behavior. For example, several weeks are required to activate mounting in all castrates by daily injection of high dose EB [30], whereas this is achieved more quickly with Silastic tube implants [35].

It is also important to note that many factors influence normal sexual behavior in rats; for example, housing condition (e.g., the number of animals per cage [36]), previous sexual experience [37], and the strain of the animal [38]. Undoubtedly these variables can influence how much sexual behavior can be restored by E after castration in male rodents.

In Suppl. Table 2, we review studies on 24 tetrapod species, excluding rats. In 18 of these species, 12 of which are mammalian, E elevated sexual interest after castration, as indicated by copulatory and/or courtship behaviors. Studies to date with castrated amphibians fail to indicate that E restores sexual activity [39–41]. Of note, though the E dose used in those studies was very high and the authors reported some mortality associated with the treatment. Whether lower E doses or a different type of E (only E2 has been tested) would produce different results needs further clarification. It is also possible that a complete restoration of sexual behavior in amphibians does not depend solely on gonadal steroids. For example, in castrated newts E only restored courtship behavior in combination with vasotocin [42].

Studies in reptiles and avian species show more inconsistent results. Only in castrated green anole lizards, chickens and Japanese quails, does E treatment increase copulatory behavior (see Suppl. Table 2). However, in other reptilian and avian species, E increased courtship behavior but not copulatory behavior. These observations suggest that some sexual interest can be restored by E in castrated males of these species. The only exception is the zebra finches, in which neither copulatory nor courtship behaviors have been restored with E administration. However, this could be dose-related as the implant used in that study had a relatively small volume compared to the implant used in Japanese quails. In fact, Watson et al. [43] showed that restoration of sexual activity in castrated quails by E is dose-dependent. To date, different doses of E have not been tested in castrated zebra finches.

As shown in Suppl. Table 2, the majority of mammalian castrated males (12 out of 13 species, excluding rats) increase sexual activity above castrate level following E treatment. The only exception is the rhesus monkeys [44,45]. However, this could be dose-related as high EB doses (higher than 5 μg/kg/day) cause penile, scrotal sac and perineal edema in rhesus monkeys [45]. E-induced genital edema was also observed with baboons injected with EB [46] and rhesus monkeys with estradiol dipropionate [47], but not in chimpanzees receiving oral α-estradiol or ethinyl estradiol [48,49]. These findings suggest that the swelling of peripheral tissue in some castrated male primates given supplemental E may be associated with the method of administration or the type of E compound used. This warrants further investigation since different E compounds activate sexual behavior in other mammals where E2 fails to restore copulatory behavior after

castration; e.g., in guinea pigs (compare [50] and [51]) and in rabbits (compare [52] and [53,54]) estrone, but not EB, can elevate sexual interest after castration.

Similar to what has been observed with rats, studies with other species have shown that various factors contribute to how much sexual behavior can be restored after castration. Once again, relevant factors include age at castration [55], type of E compound [56], and method of administration [57]. Additionally, lighting conditions can be crucial for those species whose sexual activity varies seasonally in their natural habitat. For example, in green anole lizards, E increased copulatory activity when the amount of light per day increases, resembling the Spring season, but not under Fall lighting conditions [58]. Other factors, such as the duration of the treatment, become important when daily injections are used (see results in deer mice [59] and in golden hamsters [60,61]). This is because, as previously mentioned for rats, with daily injections it takes several weeks to elevate plasma E2 levels to those of proestrous females [34]. Therefore, if this method of administration is used, experimenters should consider assessing the sexual behavior multiple times over several weeks, as the effects of E may require a prolonged time to be optimized. In sum, E can increase sexual activity in castrated males from a variety of tetrapod species and many factors contribute to how much sexual interest can be elevated by E.

3.2. Human studies

E has been administered to genetic males who are androgen (and/or E) deprived [8]. High doses of E reduce libido in intact men because E shuts down the hypothalamic–pituitary–gonadal axis by enhancing negative feedback inhibition [62]. On the other hand, E may increase the libido of hormone-deprived men above castrate levels.

In Table 1, we review studies on prostate cancer patients who were on E-therapy. In those studies, there was always a subset of patients who maintained erectile function following PCa treatments, however, what determines if erectile potency can be preserved is not known. It is also important to add that erectile function does not always translate into the patients being sexually active. In Ellis and Grayhack [63] and Choi et al. [64], 38 and 19 patients, respectively, were sexually potent prior to any treatment but only 26 and 7, respectively, were sexually active (more than 13 coitus/year) after treatment. Thus, pre-treatment sexual behavior may influence whether patients remain sexually active after treatment.

In two studies [63,65], some men were sexually active prior to treatment and among these men, more patients on E therapy remained sexually active than those who were orchiectomized. Ellis and Grayhack [63], however, only assessed sexual activity based on penile–vaginal intercourse. This was not the case in the Bergman et al. [65] study as only 2 out of 12 patients retained erection. In contrast, Bergman et al. [65] reported that 7 out of 10 E-treated men continued sexual activity even in the absence of orgasm. Petersen [66] found that 8 out of 38 patients retained libido and 3 out of 26 patients maintained coital activity after E treatment, but the author did not mention if the patients were involved in non-coital sexual activity. In sum, there is evidence that E-treated PCa patients tend to be more sexually active than castrated men who are not on E-therapy. However, a more thorough study needs to be conducted to assess how libido is affected in these patients and whether these patients continue non-coital sexual activity in the absence of erectile and/or orgasmic function, which can be indicative of sexual interest even when coital sex is unlikely.

There is evidence that E can raise sexual interest in other populations of androgen-deprived men. For example, in men castrated for other reasons than PCa E elevates libido above castrate levels; in fact almost as well as when the subjects are taking testosterone [67,68]. Furthermore, many male-to-female transsexuals (MtFs) on E therapy remain sexually active [69,70], but these studies are hard to compare as many MtFs concurrently take progesterone and/or antiandrogens.

Some relevant data are available on yet another group of men; those who have low E plasma levels as a result of an aromatase gene mutation. These men have a normal libido but in one case study, E treatment elevated the patient's sexual interest [71], while in three other case studies, E therapy alone did not change the patients' libidos [72–74]. However, this could be because testosterone is still endogenously produced in these patients.

Further evidence for E's role in maintaining libido comes from studies on PCa patients who are on antiandrogen monotherapy for ADT. Antiandrogens prevent the binding of testosterone to androgen receptors. The unbound testosterone is then converted to E by the enzyme aromatase. Therefore, PCa patients, who receive antiandrogen treatment, have an elevated plasma E2 level secondary to elevated serum testosterone levels. Some studies report that more patients on antiandrogen monotherapy retain their libido than those who are surgically castrated [75–77]. In one report, over 60% of patients taking antiandrogen monotherapy preserved their sexual interest as compared to ~30% of patients who were surgically castrated [78]. Here, the preservation of libido by antiandrogens is understood to be due to elevated E2 levels, and it is notable that these men experience other estrogenic effects, such as gynecomastia and reduced hot flashes.

Similar to animal studies, the effectiveness of E in restoring libido for men may depend on multiple factors. Age is an important one as sexual performance declines naturally as men age [79]. Pre-castration sexual behavior should also be considered as some patients, even though they have a partner and normal erectile function, are not sexually active. Thus, they would remain sexually inactive after treatment. At the other extreme, some people are naturally hypersexual, thus, they retain high sexual activity after treatment. For example, in the Ellis and Grayhack study [63], there was a man who claimed having intercourse 6 times per night pre-operatively. After castration and E treatment, he still reported having intercourse 15 times per week though it declined to twice per week

Table 1
The effect of estrogen therapy on the sexual behavior of prostate cancer patients.

Study	Sample size	E type and dose	Selected results	Additional notes
Ellis and Grayhack [63]	20 (E alone) 41 (castration + E)	Stilbestrol at 3–500 mg per day and chlorotrianisene at 12.5–25 mg per day [both are synthetic E]	7 (E alone), 6 (castration + E), and 3 (castration only) patients retained potency after treatment. Among these patients; 4 (E alone), 2 (castration + E), 2 (castration only) remained sexually active—having intercourse more than once a month.	Before treatment, 9 (E alone), 22 (castration + E), and 7 (castration only) patients were sexually potent but only 26 were sexually active. The authors did not indicate how these 26 were assigned into treatment groups. Those who were impotent before treatment remained impotent after treatment.
Choi et al. [64]	10 (E alone) 22 (castration + E)	2 mg of diethylstilbestrol per day	6 (E alone), 4 (castration + E), and 1 (castration only) patients retained potency after treatment. After treatment, those (regardless of treatment) that remained potent had a reduced frequency of sexual intercourse with a mean of 9.4 times in a year.	Before treatment 9 (E alone), 7 (castration + E), and 3 (castration only) patients were sexually potent. Before treatment those (regardless of treatment) that were potent had a mean sexual intercourse frequency of 16.4 times in a year.
Bergman et al. [65]	12	Intramuscular injection of 80–160 mg polyestradiol phosphate per month and 150 μg ethinylestradiol per day	Among E-treated patients, 5 patients found their libidos were preserved, 2 had reduced libidos, and 5 completely lost their libidos (compared to 5, 4 and 3, respectively for orchiectomized men). 8/10 patients receiving E treatment remained sexually active with a partner compared to 3/10 for orchiectomized men.	Only men who had erections and were sexually active (either by intercourse or masturbation) before treatment were included in the study.
Petersen [66] – this study included the data from Hauser [172] and Petersen [173] as well	50	45 patients were on intramuscular injection of 80 or 160 mg polyestradiol phosphate per month. 5 patients took high dose [total dose received was between 270 and 2000 mg] estradiol dipropionate; one of the 5 took additional ethynil estradiol.	8/36 retained some libido 6/41 were capable of erections 2/40 were capable of ejaculating 3/26 maintained coital activity	Only 41 patients had partial/full sexual function before treatment.

30 months later. Other factors, which may confound the effect of E on sexual interest, include stress levels and socio-cultural factors.

4. Orgasmic function

In both men and women, the pelvic floor muscles (PFM) are important for continence and orgasm. These muscles contract rhythmically during orgasm in both men and women [80,81]. Changes in the PFM after ADT have not been widely researched in humans, but in animal studies, castration causes atrophy of the PFM, suggesting their dependence on androgens. In fact, the PFM contain both androgen and estrogen receptors [82]. However, E cannot prevent castration-induced atrophy; although one study on male rats showed that E treatment partially maintains the morphology of the pubococcygeous muscle after castration [83].

In rats, one PFM (the bulbocavernosus) is innervated by the spinal nucleus of the bulbocavernosus (SNB) and the cell bodies of the motoneurons in the SNB atrophy after castration. E cannot reverse this shrinkage [84,85]. However, E maintains the normal electrical activity of the PFM in castrated male rodents [86–88]. These findings suggest that E may have some role in normal function of the PFM. In fact, high dose E treatment restores ejaculatory behavior in castrated male rats [30]. Such findings may not translate into restoration of erectile function in androgen-deprived men, but they do not exclude the possibility that E has an effect on orgasmic function.

Unfortunately, there are few studies on how E may affect orgasm in men. Bergman et al. [65] found that 11 out of 12 PCa patients lost their ability to reach orgasm following E

therapy. Of note, the age of the men in that study ranged from 64 to 87 years, old enough to experience the natural decline in orgasmic capability that occurs with aging [79]. As previously reported, ADT may not always lead to loss of orgasm [3,89]. In the report by Wassersug [89], the subject was able to reach orgasm using alternative sexual practices that did not depend on penile erections.

5. Skin sensitivity

Women appear to have more sensitive skin than men [90,91]; at least on the hands [92], nipples, areolas and breasts [93]. This sex difference only appears at puberty, suggesting that this is due to either the high testosterone in men or high E in women. In one study [92], a higher plasma E2 level in women was associated with increased sensitivity to vibrotactile stimulation on the hand. Therefore, E may have a direct influence on skin sensitivity.

In males, aromatase and ERs are expressed on the skin of the genitals, sensory corpuscles and penile nerves [94–96] suggesting E's involvement in afferent input and potentially in sexual arousal. As further support of this idea, ERs are present in the autonomic and sensory ganglionic neurons that are associated with male genitalia [97,98].

In castrated male rodents, the receptive field of the nerves that supply the perineal region is reduced [99] and there are changes in the physiology of the genital skin mechanoreceptor [99,100]. However, no changes in the genital sensory afferent activity after castration have been reported in the one other mammalian species examined to date; i.e., the cat [101]. Currently, we do not know if E increases the size or sensitivity of the sensory field of the genital skin in castrated human males. However, two independent studies [102,103] showed that E treatment to ovariectomized rats widens the sensory field of the genital skin, which may be beneficial in increasing sexual arousal by tactile stimulation. The effect of E on the female skin's receptive field is not restricted to genitalia, but has been replicated in facial [104] and trigeminal [105] neurons. Furthermore, the effect of E on trigeminal neurons was not exclusive to females and was also observed in castrated male rats [106]. If E increases tactile sensitivity to genital skin, it may potentially help increase sexual arousal associated with tactile stimuli of an erotic nature.

6. Pros and cons of estrogen therapy

6.1. Advantages

6.1.1. E reduces hot flashes and may improve sleep

Hot flashes and night sweats are reported by 70–80% of men who are on ADT and the majority of these cases are severe enough to warrant intervention [4,107]. In some studies, E has been proven to be one of the most effective agents to reduce the severity of hot flashes in men on ADT [108–111].

Severe hot flashes often lead to sleep problems [112,113]. Sleep disturbance in patients can also interfere with the sleep of their partners, impacting the couple's quality of life. Whether E can improve sleep quality in PCa patients on ADT is unknown. However, indirectly, sleep quality should improve if E reduces nocturnal hot flashes. In one study of MtFs [114], E in combination with antiandrogens prolonged one of the sleep stages, but the authors did not report whether the individuals subjectively reported better sleep quality.

We recently explored the effect of E2 administration on the sleep/wake behavior of castrated male rats [115]. We found that E treatment promotes wakefulness and helps recover some sleep following sleep deprivation. If E can improve daytime alertness and help androgen-deprived men sleep better, it could indirectly also reduce the cognitive decline that has been reported with ADT in several studies [116,117].

6.1.2. E protects bone

ADT induces bone resorption. This appears to be due to both androgen and estrogen deprivation, since receptors for both steroids are present in the skeletal system and are involved in bone mineral balance [118]. ADT reduces bone mineral density most rapidly shortly after ADT is started [119] and fracture incidence increases as well [120,121].

High dose E therapy, as a primary method for ADT, has been shown to maintain and improve bone mineral density in PCa patients [5,122]. This finding was not replicated in patients who had previously been treated with LHRH agonists [123]; however the E dose used in that study was low compared to the other two studies.

6.2. Critical period hypothesis

The interval from starting ADT to the beginning of E treatment may be crucial in maximizing the beneficial effects of E. This is based on the "critical period" [124], which is also called the "window of opportunity" [125], hypothesis on the cognitive performance of post-menopausal women on hormone replacement therapy. Based on this hypothesis, E treatment started in the perimenopausal period can be cognitively protective, but the benefits may be reduced or even lost with later administration. Data from ovariectomized rodents further support this hypothesis; i.e., female rats perform better on cognitive tasks when treated with E early rather than late after gonadectomy [126]. Brinton [127] proposed a "healthy cell bias" hypothesis to explain this timing effect. In brief, neuronal function deteriorates naturally with age and/or after steroid deprivation, but E treatment can be neuroprotective when administered before there is substantial neuronal degeneration.

The effect of ADT on cognition has been controversial. While some studies found that cognition declines in certain domains after ADT [128,129], an improvement or no change in cognition following ADT has also been reported [116,117]. It has been previously suggested that these divergent results

for men on ADT may be in part explained by the critical period hypothesis [130].

A few studies have explored the effect of E on cognitive function in androgen-deprived genetic males, but with mixed results. One study showed that E treatment improved at least one cognitive domain in PCa patients on ADT [7]. Similar data are available for MtFs [131,132]. However, these findings were not supported in two other studies [133,134]. It is important to note that the plasma E2 levels in those two studies were not as high as those in the Beer et al. [7] study. Thus, the difference in results could be dose-related. Whether the timing onset of E treatment after ADT is important in maximizing its effect on cognition is not known, however, that has previously been suggested to account for these divergent results [130].

We recently explored the critical period hypothesis as applied to the sexual behavior of castrated male rats [9]. We found that late (i.e., 3 months delay in) E2 treatment after castration was as effective as early (i.e., no delay) E2 treatment in restoring sexual interest (indicated by mounting behavior) in male rats. This finding is consistent with the study by Antliff and Young [50] who compared the effect of early (1 week) versus late (10 weeks) initiation of estrone treatment after castration on the sexual behavior of male guinea pigs. Therefore, the effects of E on male sexual behavior may be relatively insensitive to when E treatment is started after castration.

6.3. Disadvantages

6.3.1. Cardiovascular morbidity

After Huggins and Hodges [135] discovered that estrogen (E) treatment reduces the serum acid phosphatase level in PCa patients, oral E became the first drug treatment for PCa. Oral E, however, elevates thromboembolic risk and was subsequently replaced with LHRH agonists [136]. Yet, LHRH agonists increase the risk of metabolic syndrome [137], which may carry its own cardiovascular morbidity risk [138,139].

Recent studies [140,141] have determined that the thromboembolic risk of E can be reduced if the drug is administered parenterally. This is because when E is administered orally, the E is carried by the portal system directly to the liver and undergoes hepatic metabolism resulting in the up-regulation of clotting factors [142]. However, this surge to the liver can be avoided when E is administered parenterally; i.e., transdermally or through intramuscular injection.

A high plasma E2 level may increase cardiovascular morbidity. However, data to date suggest that this risk is not higher than that associated with LHRH agonists [140,143,144]. One study suggests that this risk is only during the first two years of treatment and in the long term, E may reduce cardiovascular morbidity [145]. In addition, there is evidence that E can be cardioprotective through activation on its G-protein coupled receptors [146]. Furthermore, parenteral E administered to androgen-deprived PCa patients has also been shown to improve their lipid profiles [6]. Recently, Scott et al. [147] reviewed evidence showing that there is a critical period for E to be beneficial for cardiovascular function in post-menopausal women. Whether this is true for androgen-deprived men is uninvestigated.

6.3.2. Gynecomastia

E therapy in genetic males causes gynecomastia, which has both psychological and social implications [148,149]. This is a desired effect for MtFs, but considered undesirable by most PCa patients. Interventions for gynecomastia are available and include subcutaneous mastectomy and the use of prophylactic breast radiation [148]. In addition, selective estrogen receptor modulators, such as tamoxifen, have been recommended to counteract gynecomastia [150]. Although tamoxifen can be effective in reducing this specific side effect of high E, those authors do not consider the positive benefits of E on other organs and tissues, most notably bone and the brain.

6.3.3. Breast cancer risk

Although men have a relatively lower risk than women, high dose E still elevates their risk of developing breast cancer [151]. So far, there are only 6 reported cases of bilateral breast cancer in PCa patients on E [152]. Risk factors for men to develop E-sensitive breast cancer are not well known. Thus, regular breast cancer screening should be considered for genetic males on E therapy.

6.3.4. Prostate cancer risk

E appears to be active in a castration resistant state of PCa [153–158], although it is controversial as to whether E has a stimulatory or inhibitory effect on PCa cells [159]. How E may potentially promote carcinogenesis of PCa at the cellular level has recently been reviewed and the activation of ERα, but not ERβ, is thought to underlie this effect [160,161]. In addition, E may also activate mutated androgen receptors [162,163]; as has been observed with antiandrogens. If that happens, the use of E as a PCa treatment should be discontinued.

6.4. Treatment regime

E exposure can induce the autoregulation of ERs by regulating their degradation [164,165]. For example, high plasma E2 levels lead to the degradation of ERs, which is presumed to be the mechanism that maintains an optimal cellular response to E2 in, for example, premenopausal women. Based on this, the effect of E is likely to be reduced under chronic E administration because the ERs will be down-regulated. For this reason, we hypothesize that cyclical administration of E would be a better option than continuous dosing. Consistent with this suggestion is the fact that intermittent LHRH agonist therapy attenuates the detrimental side effects of ADT (including some sexual recovery when the treatment is stopped) and therefore improving the patients' quality of life [166,167]. In a small retrospective report on intermittent

diethylstilbestrol (DES) therapy, Klotz et al. [168] reported that 10 out of 12 men became impotent while on DES therapy, however, 9 resumed sexual activity following the cessation of DES therapy. Based on these findings, intermittent or cyclic E therapy may be preferable to continuous therapy for maintaining sexual interest.

7. Implications for future research

Many questions remain about the effects of exogenous E on androgen-deprived men. For example, the critical period hypothesis has not been explored for men in terms of how the timing of administration may influence E's ability to preserve libido or cognitive function. Further research is needed in general to determine: (1) what factors influence the extent to which libido can be preserved by E in androgen-deprived males, (2) how E maintains orgasm in some castrated men in the absence of erectile function, and (3) whether E can increase arousal by improving genital skin sensitivity.

What also remains to be explored is whether E can improve sleep quality and reduce fatigue in men on ADT as has been shown for rats in one laboratory study [115]. Furthermore, whether the beneficial effects of E in androgen-deprived males can be enhanced with cyclic or intermittent dosing is uninvestigated.

8. Conclusion

Estrogen plays a role in normal male physiology. Declining plasma E levels in men after ADT lead to adverse events, such as hot flashes, reduced libido, and osteoporosis. We suggest that PCa patients, who are prescribed androgen suppression to treat androgen dependant PCa, could be offered supplemental parenteral E2 (avoiding the thomboembolic risk of oral E) to attenuate the detrimental side effects of E deprivation. However, this offer should be made with caution and avoided if the patient has a family history of E sensitive breast cancer or a personal history of thromboembolic events.

Based on the studies reviewed above, we expect that exogenous E administration can raise libido above castrate levels in some men on ADT. This residual libido may be appreciated not only by the patients, but also their partners.

Both patients and their partners should be counseled about the pros and cons of parenteral E2 as either a supplement to LHRH agonists, or as a primary method of ADT. They need to understand, for example, the merits in preserving the patient's libido, even if erectile function is not recovered. Patients and their partners need to be informed that sexual intimacy is still possible with erectile dysfunction, and that there are options of rewarding sexual activity in the absence of penile-insertive intercourse [89,169]. Patients further need to know that their partners may still appreciate physical contact in the absence of coital sex [170]. Having some libido preservation in the male on ADT can thus help couples maintain intimacy of both a sexual and nonsexual nature.

Estrogens are currently prescribed to PCa patients as second line hormonal therapy [171]. We suspect, however, that supplemental E2 will be most effective in preserving the quality of life of PCa patients, if provided earlier in treatment, concurrent with the initiation of ADT. Lastly we speculate that E's effectiveness may be enhanced if it is administered in a cyclic fashion that preserves ER density on target tissues.

Conflict of interest

None.

Reviewers

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Acknowledgements

We thank Hannah Calich and Imhokhai Ogah for proofreading the manuscript. Kirsten Kukula and Inga Westermann translated the German papers. Sook Hyun Chung translated a Korean paper. We also thank Paul Schellhammer, Celestia Higano, Imran Shah for critical feedback on the draft manuscript.

Erik Wibowo was a recipient of a Cancer Research Training Program award from the Beatrice Hunter Cancer Research Institute in conjunction with the Canadian Cancer Society, Nova Scotia Division. He is also supported by a Scotia Support Grant through the Nova Scotia Health Research Foundation. Richard Wassersug's research has been supported by the Nova Scotia Health Research Foundation, the Beatrice Hunter Cancer Research Institute, and the Natural Science and Engineering Research Council of Canada. The funding sources were not involved in the literature search, writing the article, or deciding to submit the article for publication.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.critrevonc.2013.01.006. Refs. [174–260] are cited in Supplementary Tables.

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Biographies

Erik Wibowo graduated from the University of Sydney with a Bachelor of Medical Science (Honors) in 2008. As an undergraduate he investigated the neuroanatomy of the hearing mechanism in amphibians and reptiles and published on that in the *Journal of Comparative Neurology* (Wibowo et al., 2009; *J. Comp. Neurol*. 516:74–85). Erik pursued graduate studies at Dalhousie University under the supervision of Drs. Richard Wassersug and Kazue Semba. There, he has studied how estrogen influences sleep quality and sexual behaviors of castrated male rats as a model for prostate cancer patients on androgen deprivation therapy. The results of his sleep study have now been published (Wibowo et al., 2012; *Behav. Brain Res.* 226:456–64). The sexual behavior study has also been published in *Physiol. Behav.* (2013;110–111:63–72). Erik is now exploring the cellular mechanisms behind how estrogen modulates sexual behavior in male rats. As a graduate student, Erik has received funding from the Faculty of Graduate Studies and the Department of Anatomy & Neurobiology at Dalhousie University, the Canadian Cancer Society through the Beatrice Hunter Cancer Research Institute, and the Nova Scotia Health Research Foundation. Following his Ph.D., he intends to continue research on male sexual health.

Richard Wassersug, Ph.D., is an Adjunct Professor in both the Department of Urologic Sciences at the University of British Columbia and the Australian Research Centre in Sex, Health and Society, La Trobe University. Recently he retired from Dalhousie University as a Full Professor in the Department of Anatomy & Neurobiology. Dr. Wassersug is currently helping to design a comprehensive survivorship program in Vancouver for prostate cancer patients and their partners. Dr. Wassersug has published more than 200 peer-reviewed articles. In his earlier career, his research largely centered on the biology of amphibians. More recently his focus has been on the psychology of androgen deprivation in various populations ranging from advanced prostate cancer patients to male-to-female transsexuals. Some of this research is in collaboration with his doctoral student, Erik Wibowo. Together, they have co-authored five peer-reviewed articles. In the past decade Dr. Wassersug's research has been funded by the Natural Sciences and Engineering Research Council of Canada, the Canadian Institutes of Health Research, Parks Canada, the Dalhousie Medical Research Foundation, the Prostate Cancer Foundation of British Columbia, the Beatrice Hunter Cancer Research Institute, and more recently the Nova Scotia Health Research Foundation.